cytokines IL-2 and IL-4, particularly of IL-4, by NOD thymocytes and peripheral T cells. For example, Figure 4 shows the stimulation of IL-4 secretion in these cells.

These cytokines are known to be associated with an increase of the Th2 T cell phenotype, relative to the Th1 phenotype. Such a shift in T cell phenotype has a beneficial effect and inhibits cell-mediated immunity in many autoimmune diseases, regardless of the particular antigen which provokes the disease. See, for example, Saoudi et al. (1993), Eur. J. Immunol., v. 23, pp. 3096-3103. A number of autoimmune diseases, including rheumatoid arthritis, multiple sclerosis and lupus erythematosis, are associated with a reduction in Th2 phenotype and in Th2-associated cytokines (see, for example, Ekerfelt et al. (2001), Clin. Exp. Immunol., v. 123, pp.112-118). Since amelioration of an autoimmune disease by stimulation or increase of the Th2 phenotype is a mechanism common to many autoimmune diseases, the inventor's finding that treatment with an agonist anti-CD28 antibody inhibits development of autoimmune diabetes and is accompanied by such a change in T cell phenotype would indicate to one of ordinary skill in the art that the method of the invention is applicable to preventing the development of autoimmune diseases in addition to autoimmune diabetes.

It is therefore respectfully submitted that claims 1 to 6 and 8 to 9 are fully enabled by the specification as filed.

The Examiner comments that Thompson found opposite effects in diabetes and multiple sclerosis using antibodies to B7.2. The studies reported in Thompson were carried out by different groups, using different antibodies. As discussed in the specification as filed, at page 8, lines 12 to 16, not all antibodies to CD28 will function as agonists to activate CD28. The claims are directed to preventing the development of an autoimmune disease by administering a T cell CD28 co-stimulatory receptor agonist.

One of ordinary skill in the art would be aware, from reading the specification, that an agonist antibody had to be selected and anti-CD28 antibodies can readily be screened for agonist activity by a T cell proliferation assay such as that described in the specification, as discussed at page 8, lines 27 to 29.

Furthermore, it is respectfully submitted that it is not valid to compare effects seen with anti-B7.2 antibodies and draw conclusions about what would happen using anti-CD28 antibodies, due to the different roles played by CD28 and B7.2 in autoimmune diseases and particularly due to the differences in expression between CD28 and B7.2. CD28 is constitutively

expressed on T cells throughout the autoimmune disease process and even before the initiation of autoimmune disease and this expression is common to all autoimmune diseases. In contrast, B7.2 is expressed only after immune cell activation and then only on antigen-presenting cells in specific tissue areas affected by the inflammatory insult (Weintraub et al., (1997), J. Immunol., v. 15a, pp. 4117-4126; Karandikar et al., (1998), J. Immunol., v. 161, pp. 192-199).

As a result, the profile of tissue B7.2 expression differs dramatically from one autoimmune disease to another. It is therefore not surprising that treatment with anti-B7.2 antibodies may be effective in one autoimmune disease and not another, as reported by Thompson. It is not valid to conclude from studies on treatment with anti-B7.2 antibodies, as does the Examiner, that the efficacy of treatment with antibodies to CD28, which is expressed on T cells in all autoimmune diseases, will be similarly unpredictable.

¶11. Claims 1-6, 8, and 9 were rejected under 35 U.S.C. §112, first paragraph, on the grounds that while the specification enables a method for preventing development of autoimmune diabetes in the NOD mouse, it allegedly does not reasonably provide enablement for a method for preventing autoimmune diabetes in humans.

The Examiner argues that one skilled in the art would not have recognised that a method of preventing diabetes in the NOD model system could be applied as a method of preventing autoimmune diabetes in humans "because genus-specific differences were well known to the skilled artisan at the time the invention was made". The Examiner points to a paper by Bowman et al. (Immunology Today (1994), v. 15, pp. 115-120), regarding the genetic homogeneity of the NOD mouse, as contrasted with the genetic heterogeneity of humans.

It is respectfully submitted that the Examiner mis-characterizes the teachings of Bowman.

In fact, while Bowman does certainly comment on the genetic homogeneity of the NOD mouse and on the genetic heterogeneity of human beings, there is no suggestion in the paper that for that reason, or for any other reason, the NOD mouse does not provide a suitable model for the counterpart human diabetes. In fact, the Abstract concludes with the sentence "in this article, Mark Bowman, Edward Leiter and Mark Atkinson review the intervention strategies that prevent IDD in the NOD mouse and indicate why these studies may well be relevant to the prevention of IDD in humans."

Similarly, the conclusion paragraph, at page 119 of the article, states that "the NOD mouse has provided a model system to study not only the pathogenesis and natural history of a disease that is similar to human IDD, but also means with which to test intervention protocols that could be used to prevent the disease in humans."

It is well known to those of skill in the art that the NOD mouse is an accepted model system for treatments which, when found efficacious in the NOD mouse, go on to clinical trials in human beings. For example, a Diabetes Prevention Trial has recently been carried out, applying in clinical trials in humans treatments previously noted to be effective in preventing the development of diabetes in the NOD mouse. See, for example, Yu et al., (2001), Diabetes, v. 50, pp. 1735-1740.

The murine model is a useful tool in the identification of candidate therapies due to the distinct similarities between human and murine autoimmune diabetes progression. These similarities include (i) the strong genetic association of autoimmune diabetes in both species with their respective loci of the major histocompatibility complex, (ii) the presence of insulitis (lymphocytic infiltration) in the pancreatic islets of both species, (iii) the development of a multi-specificity B cell response and secretion of auto-antibodies against islet cell antigens and (iv) the modulating effects of cyclosporin A on the disease in both mice and humans.

As outlined in Bowman et al., both humans and NOD mice undergo a very similar disease process with distinct similarities in the disease pathology (page 115, Para 1). Furthermore, the disease progression is mediated by similar types of immune cells in both, identical self-proteins (autoantigens) being the target of B and T cell activities in both species. These autoantigens include insulin and glutamic acid decarboxylase (GAD). Many therapeutic regimens validated in the NOD mouse have progressed to human clinical trials for the therapeutic treatment of autoimmune disease. These include treatments with anti-insulin antibodies and anti-GAD antibodies. These trials indicate that those of skill in the art consider that disease progression in the NOD mouse is reflective of human autoimmune disease and that successful therapeutic intervention in the NOD model is applicable to human therapy.

The Examiner further argues that in order to have a reasonable expectation of success in preventing the development of diabetes in humans, a skilled artisan would have to be able to clearly identify both that an individual was at risk and that the disease had not already progressed beyond a window corresponding to the two-four week period in the NOD mouse. In fact, several clinical methods are available to screen humans and identify those at risk of developing Type I

diabetes. These methods include looking for specific genetic haplotypes pertaining to DR and DQ alleles of MHC II or conducting serological assessment of candidate human subjects for the presence of antibodies against Type I diabetes-associated autoantigens such as insulin, GAD, etc. Such clinical markers were utilised to identify pre-diabetic patients for the purposes of the above-mentioned Diabetes Prevention Trial.

Accordingly, it is respectfully submitted that claims 1 to 6 and 8 to 9 are fully enabled by the specification as filed.

Withdrawal of the rejections of claims 1-6, 8, and 9 under 35 U.S.C. §112, first paragraph, is respectfully requested.

Rejections under 35 U.S.C. §103

¶14. Claims 1-4 were rejected under 35 U.S.C. §103(a), as allegedly being unpatentable over Rabinovitch in view of Lenschow et al., and further in view of either King et al. or Webb et al.

The primary reference, Rabinovitch, teaches that stimulation of the immune system, so as to favour T cell differentiation towards the Th2 phenotype, can prevent autoimmune diabetes development.

As noted by the Examiner, Rabinovitch does not teach or in any way suggest that such an effect could be produced by a CD28 agonist.

Lenschow describes that blocking of signaling through CD28 produces an increased incidence of diabetes in the NOD mouse. There is no demonstration in this paper that ligation of the CD28 receptor in the NOD mouse would lead to an opposite effect, namely prevention of development of diabetes. The relevant pathways involved in upregulation of the Th1 phenotype due to blocking of the CD28 receptor and in upregulation of the Th2 phenotype by stimulation of the CD28 receptor are quite different and one skilled in the art would not conclude, from an observation on the effects of blocking CD28, that the opposite effect would necessarily apply and that stimulation of CD28-mediated signaling would be capable of preventing autoimmune diabetes in the NOD mouse.

King et al. discusses that CD28 ligation in vitro using peripheral blood mononuclear cells mediates secretion of IL-4 and IL-5. The authors did not demonstrate the effect of CD28 ligation in any in vivo environment or disease condition. The reference pertains only to peripheral cells derived from healthy humans and does not indicate relevance to cell populations of individuals suffering from autoimmune diabetes, or predicted to be at risk of autoimmune diabetes. It is not obvious from this publication that treatment with an anti-CD28 agonist in the much more complex in vivo situation would be effective to treat or prevent an autoimmune disease such as autoimmune diabetes.

Webb et al. shows that CD28 co-stimulation of cord blood $CD4^+$ cells causes differentiation towards the Th2 phenotype. The cord blood cells were chosen because they are naïve and not primed against any specific antigen. This in vitro system, using these naïve cells, would not teach anyone of skill in the art that a CD28 agonist would be effective in the complexity of the in vivo and disease situation, to prevent the development of an autoimmune disease.

It is respectfully submitted that the Examiner is using impermissible hindsight, now that the inventor has for the first time shown that stimulation of the CD28 receptor in vivo can prevent the development of an autoimmune disease. One of ordinary skill in the art would not, based on the teachings of the cited references, have had a reasonable expectation of success in preventing the development of autoimmune diabetes in the NOD mouse by stimulation of the CD28 receptor.

The deficiencies of Rabinovitch are not cured by the teachings of any of the additionally cited references, whether viewed singly or in combination.

Accordingly, it is respectfully submitted that claims 1 to 4 are patentable over the cited references. Withdrawal of the rejection of claims 1-4 under 35 U.S.C. §103(a) is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the specification:

Title beginning at line 1 of page 1 has been amended as follows:

METHODS **[AND COMPOSITIONS]** FOR PREVENTING AUTOIMMUNE DISEASE

New paragraph beginning at line 3 of page 1, after the Title, has been added as follows:

This application claims priority under 35 U.S.C. §371 to PCT/CA98/00015.

In the abstract:

Abstract beginning at line 1 of new page 37 has been added as follows:

Methods are provided for preventing the development of autoimmune diseases in susceptible subjects and for prolonging acceptance of tissue transplants by administration of an agonist of the T cell CD28 co-stimulatory receptor.